Adrenocortical effects of ABP-700 in Dogs and Humans

Objective: The objective is to present the adrenocortical effects of ABP-700, a second-generation metabolically labile etomidate analogue, when administered to dogs and humans.

Background: ABP-700 induces anesthesia by acting as a positive allosteric modulator of the γ-aminobutyric acid type A ($GABA_A$) receptor. It contains an ester bond that is precisely designed to undergo rapid hydrolysis by nonspecific blood and tissue esterases resulting in a short terminal t½ ranging from approximately 13-19 minutes in dogs and 11-19 minutes in humans. Although it was specifically designed to overcome the liabilities of other IV anesthetics including adverse adrenal effects, ABP-700 is a phenylethyl-imidazole-containing agent with the potential to induce adrenal suppression by the inhibition of 11β-hydroxylase, the enzyme responsible for the production of adrenal cortisol through the conversion of deoxycortisol to cortisol. However, the 'soft-pharmacology' of the engineered ester linker in this agent was predicted to remove any adrenal effects. Studies were performed to investigate the effect of ABP-700 on adrenal function in dogs and humans.

Methods: The effects of ABP-700 were characterized in beagle dogs (n=4). To decrease animal variability in resting levels of cortisol in dogs, the hypothalamo-hypophyseal axis was suppressed with dexamethasone (0.01 mg/kg IV) two hours before the induction of anesthesia. Each dog was administered ABP-700 (3 mg/kg IV bolus and 0.5 mg/kg/min IV infusion), etomidate (2 mg/kg IV bolus and 0.15 mg/kg/min IV infusion), propofol (5 mg/kg IV bolus and 0.4 mg/kg/min IV infusion) or vehicle for 120 minutes. Following infusion of the test article, synthetic ACTH (Synacthen, 250 µg IV) was administered. Blood samples were taken every 30-60 minutes to measure plasma cortisol concentrations and the concentrations of administered anesthetic agent. Plasma levels of cortisol and excursions from baseline were compared and analyzed based on published reports in healthy dogs (Pessina et al., Acta Vet Scand 2009).

Human volunteers were screened to ensure normal morning cortisol levels while at rest. Sixty (60) subjects were randomized to either ABP-700 or vehicle at a 5:1 ratio. Reference cortisol levels were obtained the morning of dosing. Bolus IV injections of ABP-700 (0.03 mg/kg to 1 mg/kg) or vehicle were given followed by a synthetic ACTH (Cosyntropin, 250 µg IV) challenge 60 minutes later. Blood samples were obtained 60 and 120 minutes following the ACTH challenge to measure plasma cortisol concentrations along with the concentrations of the anesthetic agent. Normal response (no evidence of adrenal suppression) was defined as an increase above from the reference plasma cortisol level of at least 200 nM/L at 60 and 120 minutes (Dorin et al., JCEM, 2012).

Results: In all treated dogs, within 1.5-3 hours after the end of infusion with either ABP-700 or propofol adrenal responsiveness was normal and indistinguishable between the agents. Etomidate, however, produced a profound and durable adrenal suppression. The following day, 24 hours post-initial anesthetic administration, all treatment groups showed a similar, normal, response to ACTH.

In humans, adrenal suppression was not observed after ABP-700 administration. All volunteers tested met the definition of normal response at both the 60 and 120 minute time points following ABP-700 IV bolus doses of 0.03 to 1.0 mg/kg or vehicle.

Conclusions: ABP-700 administration showed no adrenal suppression at pharmacologically active doses in both preclinical and clinical testing. These data support the continued evaluation of this novel agent as a broadly applicable anesthetic in humans.